

Pharmacology

A- Drugs acting by enzyme inhibition

1- α -methyldopa :

inhibits dopa-decarboxylase enzyme(Used in treatment of hypertension, it is the drug of choice in hypertension during pregnancy).

2-Anti-cholinesterase:

either reversible as physostigmine and neostigmine, or irreversible as organophosphorous compounds.

3-Glucocorticoids (cortisone): *inhibits phospholipase A2.*

4-NSAIDS

e.g. Aspirin,phenylbutazone,Diclofenac....., inhibit cyclooxygenase enzymes (COX).

5-Zileuton:

inhibits 5-lipoxygenase enzyme $\rightarrow$ $\downarrow$ leukotriene synthesis, used in prophylaxis of bronchial asthma.

6-Dazoxiben:

Antiplatelet by inhibition of thromboxane A2 synthase (same mechanism as aspirin as antiplatelet).

7-Methylxanthines

e.g. theophylline and aminophylline, inhibit P.D.E (phosphodiesterase) type IV (4) $\rightarrow$ $\uparrow$ c-AMP $\rightarrow$ CNS stimulation, cardiac stimulation, V.D. and bronchodilation.

8-Disodium cromoglycate and Nedocromil sodium:

(mast cell stabilizers) Used in prophylaxis of bronchial asthma, given by inhalation, inhibit P.D.E in mast cell.

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9-Warfarin:

"oral anticoagulant", inhibits vitamin k reductase →

↓ Synthesis of prothrombin ii (2) and other coagulation factors (vii,ix,x).

10-Dipyridamole: Antiplatelet, ↓ PDE → ↑ c-AMP.

11-pentoxifylline: methylxanthine, antiplatelet, as dipyridamole.

12-Statins: antihyperlipidaemics, ↓ HMG.CO.A reductase enzyme.

13-Carbonic anhydrase inhibitors:

e.g. acetazolamide (diamox) used as diuretic (self-limiting), ↓ IOP in glaucoma, treatment of petit-mal epilepsy, as alkalinizer of urine.

14-Angiotensin converting enzyme (ACE) inhibitors:

e.g. captopril, lisinopril, enalapril, used in treatment of hypertension (drugs of choice in hypertension + diabetes mellitus), and in congestive heart failure.

15-Digitalis (cardiac glycosides):

inhibit Na⁺/K⁺ ATPase (Na⁺ pump), used in treatment of heart failure.

16-Bipyridines:

e.g. amrinone, milrinone, eroximone, inhibit P.D.E type iii (3) , used in resistant heart failure as short term therapy.

17-Proton pump inhibitors:

e.g. dmeprazole, lansoprazole. Inhibit H⁺/K⁺ ATPase (proton pump) in parietal cells, used as antisecretory (↓ HCl) in treatment of peptic ulcer.

18-Allopurinol:

xanthine oxidase inhibitors, ↓ uric acid synthesis in prophylaxis of gout.

19- MAO Inhibitors.

20-peripheral dopa-decarboxylase inhibitors (PDDI)

e.g. carbidopa and beuserazide, combined with L-dopa in treatment of Parkinsonism.

21- COMT-Inhibitors:

tolcapone and entacapone, given with L-dopa/carbidopa in treatment of Parkinsonism.

22-Sodium valproate and vigabartin:

Inhibit GABA transaminase, used in epilepsy (broad-spectrum anti epileptics).

23-β-lactamase inhibitors:

e.g. clavulanic acid, sulbactam and tazobactam, combined with penicillin to treat β-lactamase producing bacteria e.g. staph.

24-Cilastatin:

inhibits dipeptidase enzyme in renal cells to inhibit metabolism of imipenem into nephrotic metabolite (imipenem + cilastatin = tienam).

25-sulphonamides:

inhibit dihydropteroate enzyme → ↓ synthesis of dihydrofolic acid from PAPA by bacteria.

26-Trimethoprim

27-pyrimethamine

28-proguanil:

29-Methotrexate:

anticancer, inhibits dihydrofolate reductase, causes megaloblastic anemia, treated by folinic acid (=leukovorin).

30-Rifampicin:

inhibits DNA-dependent RNA polymerase.

31-Quinolones and fluroquinolones: *inhibits DNA-gyrase.*

32-Acyclovir: *Antiviral inhibits DNA polymerase.*

33-Zidovudine:

Antiviral, used in treatment of AIDS, inhibits reverse transcriptase enzyme.

B- Drugs that inhibit phosphodiesterase enzymes (P.D.E Inhibitors)

1-Selective α 1-blockers

(e.g. prazosin , they do not cause reflex
Tachycardia as they increase cAMP & cGMP)

2-Bipyridines

(Amrinone , Milrinone , Enoximone) :Inhibit PDE III (3)

3-Methyl Xanthines

(Aminophylline , caffeine , theophylline , theobromine):
Inhibit PDE IV (4)

- 1 Sildenafil (Viagra) , Tadalafil , Valdenafil used in erectile dysfunction : Inhibit PDE V (5)
- 2 Dipyridamole : anti platelet

Drugs & git

A- Drugs causing Hepatotoxicity

1 . α -methyl dopa

(α 2-agonist-antiadrenergic-used in treatment of hypertension, is the drug of choice in hypertension during pregnancy).

2. Dantrole

(direct skeletal muscle relaxant, $\downarrow$ Ca release from sarcoplasmic reticulum, life-saving in malignant hyperthermia and neuroleptic malignant syndrome , given I.V).

3. Statins e.g; simvastatin (anti-hyperlipidemics).

4. Fibrates *e.g; clofibrate (anti-hyperlipidemic).*

5. Toxic doses of paracetamol

(or if given with HME inhibitors as alcohol and phenobarbitone) due to accumulation of NABQI.

6. Colchicine *(anti-inflammatory in gout).*

7. Tolcapone *(COMT-inhibitor used in parkinsonism with L-dopa).*

8. Phenytoin *(anti-epileptic+anti-arrhythmic).*

9. Oxazolidinediones *(anti-epileptic in petit-mal epilepsy).*

10. Sodium Valproate *(broad-spectrum antiepileptic).*

11. MAO-inhibitors *(anti-depressants).*

12. Halothane *(inhaled general anaesthetic).*

13. Tetracyclines *(antibiotics).*

14. Sulphonamides *(anti-bacterial).*

15. Isoniazid.

16. Pyrazinamide.

17. Ethionamide.

18. Para-amino-salicylic acid.

19. Ketoconazole.

20. Griseofulvin.

21. Cis-platin (anti-cancer).

B- Drugs causing Diarrhea

1-Parasympathomimetics:

*e.g Carbachol – Bethanecol -Neostigmine
(Stimulate M Receptors in Small Intestine)*

2-Adrenergic Neurone Depressants :

*e.g Guanethidine –Reserpine
(They causes Parasympathetic Predominance)*

3-Dantrolene which is direct skeletal muscle Relaxant

4- Oral Iron :

*e.g Ferrous Fermanate & Gluconate ,May cause black or bloody diarrhea
(Some oral iron causes constipation)*

5-Magansium Oxide –Hydroxide –Trisilicate :

used as Chemical antacids

6-Metoclopramide : Antemitic & Prokinetic

7-Domperidone: Antiemitic & Prokinetic

8-Purgatives (chemical & physical)

9-Colchicine : *used in Acute gouty anhritis, may causes bloody diarrhea*

10- Erthromycin : Anthmicrobial (Diarrhea is due to prokinetic

11-Broad Spectrum Antimicrobials (especially if not completely absorbed)

*e.g Ampicillin –Tetraglclines- Chloramphenicol –Cophalosporins
(Due to Superinfection)*

12-PG-Analogues : *e.g Misoprostol (see Peptic ulcer)*

C- Drugs Causing Constipation

1-Antimuscarinic Drugs

(Anticholinergic Drug =Parasympatholytics)

e.g: Atropine –Hyoscine-Antisecretory –Antispasmodic –Atropine substitutes

2-Opiod Analgesics:

e.g Morphine –Mepridine –Loperamide-diphenoxylate (note that loperamide and diphenoxylate are not analgesics) they stimulate opioid receptors in GIT

3-Aluminum Hydroxide Gel : Act as Chemical & physical Antacid

4-Calcium Carbonate :chemical Antacid

5-Calcium channel blockers :e.g Nifedipine –Verapamil

6-Drugs Having marked

” Atropine-like Action”;e.g

-1st Generation (=sedating) Anti-histaminics as Diphenhydramine

-Disopyramide : class I-Anti-arrhythmic

-Tricyclic anti-depressants as imipramine

-Carbamazepine : Anti-epileptic

D- Drugs Causing Nausea & Vomiting

1-Opioid Analgesics : e.g Morphine ,Methadone ,Meperidine

2-Cardiac Glycosides (Digitalis) :e.g Digoxin ,digitoxin

3-Methylxanthin : e.g Aminophylline , Theophylline

4-D2-Agonists : e.g L-Dopa , Bromocriptine

5-Estrogen (oral contraceptive) causes mainly nausea

6-Cancer chemotherapy

E- Drugs causing Allergic Cholestatic Hepatitis

- 1. Carbamazepine(anti-epileptic).***
- 2. Tricyclic antidepressants (TCA's).***
- 3. Chlorpromazine (anti-psychotic).***
- 4. Erythromycin (antibiotic).***
- 5. Chlorpromazine (anti-diabetic).***
- 6. Oral contraceptives.***
- 7. Rifampicin(anti-T.B)***
- 8. H2-blockers as Cimetidine (anti-ulcer).***

F- Drugs activated by gastric acidic medium

1-Chlorazepate (Benzodiazepine: anxiolytic &hypnotic)

2-Proton Pump Inhibitors

e.g. Omeprazole (Antisecretory drugs used in treatment of peptic ulcer)

3-Sucralfate (mucosal protective agent, used to prevent recurrence)

N.B.:

Ketoconazole (Antifungal)

absorption increases in acidic medium

G- Drugs destroyed by gastric acid

1-Acid-sensitive penicillins

(e.g. benzyl penicillin, procaine penicillin, benzathine penicillin, methicillin, cloxacillin, ureido-penicillins)

2- Erythromycin

(to protect against HCL, erythromycin is given as enteric-coated tablets, or estolate ester is added to erythromycin)

H- Drugs destroyed by proteolytic enzymes (Not effective orally)

1- Polypeptide antibiotics: Bacitracin & Polymyxins

2- Polypeptide hormones:

e.g. Insulin, Growth hormone, Glucagon, ACTH, ADH (vasopressin)

cardiovascular system

A- Drugs Causing Bradycardia

1-β-blocker: e.g Propranolol ,Nadolol , Atenololetc

2-Parasympathomimetics

(Muscrinic Agonists):e.g Methocholidine ,Carbachol ,...

3-Digitalis

(The Earlist manifestation of toxicity are nausea & vomiting +Bradycardia below 60 beats /min)

4- α1 –Agonists causes reflex Bradycardia

(α1 stimulation →V.C → increase B.P →reflex bradycardia through baro receptors action)

5-General Anesthesia : e.g Halthane due to increase vagal tone

6-Some calcium channel blockers :

e.g Verapamil (due to Blocking Voltage-gated Ca channels in heart)

B- Drugs causing Postural Hypotention (Orthostatic Hypotention OR Syncope)

Nitrates as Nitroglycerine (used in treatment of Angina pectoris)

1 . α1-blockers

(phentolamine , phenoxybenzamine , BUT selective α1-blockers as prazosine cause “1st dose phenomenon”)

2. Ganglion blockers

(they cause Atropine like side effect + postural hypotention + sexual dysfunction in males)

3. Adrenergic neurone blockers:

(Guanithidine , reserpine , α-methyl dopa which causes minimal hypotension)

C- Drugs used in treatment of Postural Hypotention

1. **Noradrenaline** (IV infusion) **Catecholamine**
2. **Ephedrine** (oral & IV)
3. **Phenylephrine** (oral & IV) **Non-catecholamine**
4. **Methoxamine** (oral & IV)
5. **Midodrine** (oral)

N.B. : - All previous drugs are α_1 -agonists

-They are given by I.V. injection in case of "Acute" postural hypotension due to spinal anesthesia

-They are given orally (except noradrenaline) in case of "chronic" postural hypotension

D- Drugs used in treatment of PVD

1. **α_1 -blockers** (except ergotamine , ergotoxine , dihydroergotamine , yohimbine)
2. **β_2 -Agonists** (e.g. Nylidrin , isoxsuprine)

M3-Agonists = parasympathomimetics (e.g. Methacholine)
3. **Calcium channel blockers** e.g. Nifedipine
4. **PGI₂** : Epoprostenol
5. **Dihydroergotoxine** (the only ergot alkaloid useful in PVD)

E- Drugs contraindicated in PVD

1. α 1-Agonists

2. **Ergot alkaloids** (except dihydroergotoxine)

3. Non selective β -blockers

F- Drugs used in treatment of paroxysmal atrial tachycardia (PAT)

1. β -blockers

2. **M2-Agonists** (e.g. Methacholine, Edrophonium, Neostigmine)

3. **Digitalis** (cardiac glycosides)

4. **Anti Arrhythmic drugs** : quinidine, Ca^{2+} -channel blockers (e.g. verapamil)

5. α 1-Agonists:

e.g. Noradrenaline, phenylephrine, Methoxamine (causes reflex bradycardia following elevation of blood pressure & contraindicated in hypertensive patients)

G- Drugs contraindicated in PAT

1. **β 1-Agonists:** e.g. Adrenaline, isoprenaline, ephedrine

2. **M2-antagonists:** e.g. Atropine, Gallamine

3. α 1-antagonists:

due to hypotension followed by reflex tachycardia (except selective α 1-blockers as prazosin)

4. Arteriodilators

(e.g. Hydralazine , Minoxidil , β_2 -agonists due to reflex tachycardia following hypotension)

(Atropine is non-selective muscarinic antagonist whereas Gallamine is a competitive neuromuscular blocker that block Nm receptors and also blocks cardiac M2- receptors)

H- Drugs causing Tachycardia

1- β_1 -agonists : e.g. Adrenaline , Isoprenaline , Ephedrine

2- β_2 - agonist :

e.g. Salbutamol , Ritodrine

β_2 -stimulation lead to :V.D :decrease B.P :reflex tachycardia & may be due to β_1 stimulation by large doses because Selectivity is not absolute

3-Atropine

(antimuscarinic =parasympatholitic) , note that atropine may Cause initial bradycardia due to block of presynaptic M-receptors that cause increasing release of acetylcholine or due to stimulation of C.I.C

4-Methylxanthines :

e.g. Aminophylline , theophylline , by inhibition of P.D.E type 4 & increase C-AMP

5-Arteriodilators :

e.g. nifedipine (and other dihydropyridine Ca^{2+} Chanel blockers) , hydralazine , minoxidil , (nitrates are mainly Venodilators but may cause arteriodilatation) . Arteriodilators Cause reflex tachycardia

6-Glucagon hormone (increase C-AMP by stimulation of adenylcyclase)

7-Alpha 1-blockers :

e.g. phentolamine , phenoxybentamine , they cause

reflex tachycardia due to arteriodilatation , note that selective alpha1-blockers as prazosin cause no (or minimal) tachycardia.

8-Ganglion blockers : e.g. Trimethaphan

I- Drugs causong hypokalemia

1-Thiazide diuretics

2-Loop diuretics

3-C.A. Inhibitors

4-Steroids (Aldosterone - cortisone)

5-Adrenaline (and other drugs acting as β_2 -Agonists) due to uptake of K^+ from blood into skeletal muscles.

J- Drugs causing hyperkalemia

1 K^+ -sparing diuretics

2 ACE-Inhibitors (Captopril ,)

3 ARBs (Losartan ,)

4 Drugs that inhibit Aldosterone synthesis

(e.g. Metyropone , see hormones)

5 Succinycholine

6 Non-seletive β -Blocker

(e.g. propranolol)

N.B. Digitalis does not cause hypokalemia , but hypokalemia induces digitalis toxicity.

K- Drugs that are contraindicated in porphyria

1-Barbiturates (phenobarbitones , thiopentone ...)

2-Primidone (antiepileptic , partially metabolized into phenobarbitone)

3-Eriseofulvin(antifungal used for treatment of muco-cutaneous fungal Infection

4-Chloroquine(anti-malarial + anti -ameobic + anti-giardiasis
+anti-inflammatory in R.A .)

nervous system

A- Therapeutic uses of sympathomimetics

1 . Shock :

Adrenaline is life-saving in anaphylactic shock ,
Dopamine in hypovolemic & cardiogenic shock ,
Dobutamine in cardiogenic shock
(in Hypovolemic shock fill up then open up)

2. Acute attacks of bronchial asthma :

Adrenaline , isoprenaline (non selective) salbutamol ,terbutaline , fenoterol ,
reproterol
(short acting selective B2 agonists)

3. Prophylaxis of Bronchial asthma :

Ephedrine (non selective & CNS stimulant) ,
Hexoprenaline & Isoetharine (catecholamines)-selective B2-agonists ,
Salmeterol & formoterol (long acting selective B2-agonists)

4. Peripheral Vascular Diseases (PVD)

e.g. Raynaud's diseases
Nylidrin , Isoxsuprine

5. Uterine relaxants (tocolytics)

in contraction ring of the uterus , premature labor , threatened abortion , dysmenorrhea : Ritodrine, salbutamol , isoxsuprine : Selective B₂-agonists

Adrenaline : Non-selective

6. Vasopressors in treatment of hypotension (see above)

7. Nasal decongestants :

Naphazoline , tetrahydrozoline, xylometazoline , phenyl propanolamine , ephedrine (causes rebound congestion) , pseudoephedrine , phenylephrine , methoxamine

8. AV block (Heart block) : Isoprenaline (S.L.) , Dobutamine (I.V. infusion)

9. Nocturnal Enuresis : Ephedrine

10. Narcolepsy (Hypersomnia): Amphetamine

11. Attention Deficit Hyperkinetic Disorder (ADHD) : Methylphenidate , Amphetamine

12. Anorexigenic drugs in obesity :

phenmetrazine , diphenmetrazine , diethylpropion , amphetamine (not used)

13. Acute heart failure : Dopamine , Dobutamine , Dopexamine : I.V. infusion

14. Chronic heart failure : Prenaterol (oral)

15. Glucoma (open-angle): Adrenaline, Dipivefrin (prodrug, better than adrenaline)

16. Cardiac resuscitation in cardiac arrest : Adrenaline (intra cardiac)

17. Mydriatics for fundus examination: (α ₁-agonists as Ephedrine-Phenylephrine)

18. Paroxysmal atrial tachycardia : (α ₁-agonists as phenylephrine)

19. Hemostatics in cases of bleeding

as Epistaxis but not in hypertensive patients
(adrenaline-ephedrine-phenylephrine-methoxamine)

20. To prolong duration of local anesthetics

but not in fingers , toes & circumcision : Adrenaline , Ephedrine , phenylephrine , methoxamine

21 .Acute hypoglycemia due to overdose of insulin or oral hypoglycemic drugs:

Adrenaline (I.V. glucose is better)

B- Drugs causing Convulsions (Seizures)

1-CNS stimulants:

a-Methylxanthines (Theophylline)

b-Amphetamine

c-Cocaine

d- Atropine

e-Araleptics (brain stem stimulants)

f- Strychnine (spinal cord stimulant)

2- Morphine (by decrease release of GABA)

3-Meperidine (metabolized into normeperidine +atropine like action)

4-Aspirin (acute toxicity) due to increase Glutamate /GABA ratio

5-Chlorpromazine (major tranquilizer = Antipsychotic = Neuroleptic)

6-MAO-inhibitors

7-Lithium (anti-manic, mood stabilizer in bipolar disorders)

8-Penicillins (if large dose or intrathecal injection)

9-Carapenem e.g. Imipenem (B-lactam antibiotics)

10-Cycloserine (antibacterial _ inhibits cell wall synthesis)

11-Fluoroquinolones especially with NSAIDS & theophylline

12-Amphotericin B (polyene –antifungal)

13-Oxamniquine (*Anti bilharzial*)

14-Cardiac glycosides

C- Drugs causing psychosis

1-D2-Agonist e.g. L-dopa , bromocriptine (*antiparkinsonian drugs*)

2-Indomethacin (*NSAID*)

3-Glucocorticoides

4-Cycloserine

5-Cardiac glycosides

D- Drugs causing Depression

1- Estrogen (*oral contraceptives*)

2-Reserpine (*adrenergic neurone depressant, depletes the brain from monoamines :5HT , noradrenaline &dopamine*)

3- Alpha –methyldopa (*decrease synthesis of monoamines by decrease dopa decarboxylase*)

4-Chlorpromazine (*causes pseudo-depression*)

urinary system

A- Drugs causing Nephrotoxicity

1-NSAIDs except paracetamol(cause "**analgesic nephropathy**" due to renal V.C. by ↓ PGE and PGI synthesis).

2-Colchicine(+ hematuria).

3-Gold salts(in treatment of **rheumatoid arthritis**).

4-Vancomycin.

5-Aminoglycosides.

6-Cephalosporins.

7-Methicillin.

8-Sulphonamides.

9-Tetracyclines(especially of expired = Fanconi syndrome).

10-Amphotericin B (Anti-fungal).

11-Acyclovir(Anti-viral).

12-Demeclocycline(Anti-bacterial tetracycline).

13-Lithium(Anti-manic + mood stabilizer).

14-Methoxyflurane(inhalant general anaesthesia as halothane).

B- Diuretics causing Hypokalemia

- 1 **Thiazide diuretics** (e.g. hydrochlorothiazide)
- 2 **Loop diuretics** (e.g. furosemide, ethacrynic acid)
- 3 **Carbonic anhydrase inhibitors** (e.g. Acetazolamide, methazolamide)

C- Diuretics causing hyperkalemia = K⁺ sparing diuretics

- 1 **Spironolactone** Aldosterone antagonists
- 2 **Canrenone**
- 3 **Trimetaphane** Non-Aldosterone antagonists
- 4 **Amiloride**

D- Diuretics causing alkalosis

- 1 **Thiazide diuretics**
- 2 **Loop diuretics**

E- Diuretics causing acidosis

- 1 **K⁺ sparing diuretics**
- 2 **Carbonic anhydrase inhibitors** Cause metabolic acidosis
- 3 **Acidifying diuretics (NH₄Cl)**

F- Self – limiting diuretics

They cause acidosis leading to reabsorption of Na^+ in exchange for H^+ or NH_4^+

1 *Carbonic anhydrase inhibitors*

2 *Acidifying diuretics*

G- Diuretics causing hypercalcemia

3 *Thiazide diuretics*

4 *Non-aldosterone antagonists*

H- Diuretics causing hypocalcemia

1 *Loop diuretics*

2 *Spironolactone* (Aldosterone antagonist)

Teratogenic drugs

1-NSAIDs except paracetamol (Aspirin causes cardiac septal defect, but is the safest NSAID).

2-Benzodiazepines.

3-Barbiturates.

4-Chlorpromazine (phenothiazine antipsychotic and anti emetic).

5-Lithium.

6-ACE-inhibitors e.g. Captopril.

7- AT1_(Angiotensin) receptor-antagonists e.g. Losartan.

8-Antihistaminics e.g. Cyclizine and Meclizine.

9-Oral anticoagulants e.g. Warfarin.

10-Thiazide and Loop diuretics.

11-Phenytoin. :

12-carbamazepine.

13- Sodium valproate: antiepileptic, causes spina bifida.

14-Nitrous oxide (inhaled gas general anesthetic).

15-Sodium nitroprusside (mixed vasodilators given I.V. infusion)

16-Aminoglycosides → fetal deafness.

17-Tetracyclines.

18-Sulphonamides → hyperbilirubinemia and kernicterus.

19-Quinolones → damage of growing cartilage and arrest of growth.

20-Griseofulvin (antifungal).

N.B.

1-Morphine is not teratogenic but cause "fetal Addiction".

2-Thalidomide was used as anxiolytic / hypnotic and it caused "Amelia" = absent limbs and "phocomelia" = short limbs (thalidomide catastrophe)

Prodrugs --> Active drugs-->Active metabolite

Prodrugs:

- 1 *Inactive drugs converted in the body into active metabolites.*
- 2 *Activation usually occurs in the liver.*
- 3 *Chlorazepate is converted into active metabolite nordiazepam in the stomach by gastric acid.*

EXAMPLES:

1-Dipivefrin (used in glaucoma).

2-Phenoxybenzamine (α -blocker).

3-Hexoprenaline (selective β_2 agonist used in bronchial asthma, it is a non-catecholamine, converted to active metabolite by COMT).

4. **Minoxidil** (antihypertensive, converted into minoxidil sulphate).

5. **Enalapril, Fosinopril, Ramipril** (ACE inhibitors).

6. **Proton pump inhibitors**, e.g; Omeprazole (in treatment of peptic ulcer).

5. **Cortisone** is converted into cortisol (=hydrocortisone).

6. **Sulindac and Nabumetone** (NSAID).

7. **Ampicillin esters** (=pro-ampicillins) as Bacampicillin, Pivampicillin, Talampicillin, converted into ampicillin in liver and GIT mucosa.

8. **Chlorazepate** (Benzodiazepine).

6. **Propacetamol** → Paracetamol, given by injection.

Active drugs converted into active metabolites

1. **Phenacetin** → Paracetamol = Acetaminophen (analgesic-antipyretic).
2. **Benzodiazepines** except LOT-Nitrazepam-Clonazepam.
3. **Morphine** → Morphine-6-glucuronide.
4. **TCA's** e.g; Imipramine → Desipramine, Amitriptyline → Nortriptyline.
5. **Spirolactone** → Canrenone (Aldosterone-antagonist K-sparing diuretic).

Iatrogenic diseases

Examples of Iatrogenic (Drug-induced) Diseases

Drugs	Disease
- NSAIDS (except paraacetamol) - Glucocorticoids	<i>1- peptic ulcer</i>
- NSAIDS (except paraacetamol) - Morphine - Non-selective B-blockers (propranolol) - Muscarinic agonists,e.g:Methacholine,Carbachol,Neostigmine	<i>2- Bronchial Asthma</i>
- Glucocorticoids - oral contraceptives - Alpha1-agonists (adrenaline-noradrenaline,phenylephrine-ephedrine,phenylprop ranolamine)	<i>3- Hypertension</i>
- B1-agonist (adrenaline-isoprenaline) - Thyroid hormones - Methyl xanthines - Arteriodilators (hydralazine,minoxidil,nifedipine....) due to reflex tachycardia	<i>4- Angina pectoris</i>
- Atropine – Hyoscine - Atropine substitutes - Atropine- like drugs - ganglion blockers - vasodilators (e.g:nitrates) - Glucocorticoids	<i>5- Glaucoma</i>
- Hydralazine (arteriodilator used as anti hypertensive) - Procainamide (class I.A anti arrhythmic) - Isoniazid (anti T.B) (They cause iatrogenic SLE especially in slow acetylators)	<i>6- Systemic Lupus Erythematosus (SLE)</i>
- D2-blockers (e.g:phenothiazines as Chlorpromazine,butyrophenones as haloperidol,metoclopramide)	<i>7- Parkinsonism</i>

- Reserpine - Alpha-methyl dopa	
- Glucocorticoides (given systemically for long duration)	<i>8- Cushing Syndrome</i>
- Digitalis - verapamil - B-blockers - Methacholine	<i>9- AV block (Heart block)</i>
- Salicylates (tinnitus I the most important manifestation of salicylism) - Ototoxic drugs,e.g:loop diuretics, aminoglycosides,vancomycin - Metronidazole – Minocycline - Indomethacin and phenylbutazone	<i>10- Tinnitus Vertigo</i>

Drugs used for diagnostic tests

Drug	Diagnosis of
1-Phentolamine (non-selective α -blocker)	Sustained type of pheochromocytoma (Phentolamine cause <u>severe</u> hypotension in these patients). "Regtieve test"
2-Clonidine (central α_2 -agonist)	Sustained type of pheochromocytoma = clonidine suppression test (Clonidine <u>can't</u> suppress release of catecholamines from the tumor)
3-Methacholine (M-agonist) 4-Histamine (Autacoid)	Paroxysmal type of pheochromocytoma = provocative test (they cause hypertension in patients with pheochromocytoma instead of hypotension in other patients)
5-Ergotamine (ergot alkaloid-oxytocic-weak α_1 -agonist)	Prinzmetal (variant or vasospastic) angina. (Ergotamine causes marked coronary V.C. in these patients)
6-Adrenaline (sympathomimetic-catecholamine- β and α agonist)	Acute hemorrhagic pancreatitis (Lewi's test). (Adrenaline causes active mydriasis in this case)
7-Methacholine (M-agonist)	Bronchial asthma = provocative test (Methacholine causes marked bronchospasm and inc. bronchial secretion in these patients)
8-Edrophonium I.V. 9-Neostigmine I.M. + Atropine (Edrophonium and neostigmine are reversible anti-cholinesterases)	Myasthenia gravis
10-Edrophonium I.V.	Differentiation between myasthenic and cholinergic crisis in patients of myasthenia gravis.
11-Ampicillin	Infections mononucleosis (Ampicillin causes maculopopular rash). "See chemotherapy"

Acute toxicity of the drugs

Signs and symptoms of acute toxicity (overdose)	Drugs causing toxicity
Hallucinations (shizophrenia-like) – convulsions – hypertension – active mydriasis – coma and finally inhibition of R.C.	1-Amphetamine 2-Cocaine
Mania – hallucinations – convulsions –hypertension followed by hypotension –hyperpyrexia – bradycardia – nausea & vomitting – coma and finally inhibition of R.C.	Ergot alkaloids (Ergotism) due to overdose of ergotamine or eating rye grains infected by ergot fungus.
Bradycardia – hypotension – bronchospasm and increased bronchial secretion – excessive secretion – diarrhea – urination – miosis – skeletal muscle twitches followed by paralysis – convulsions – followed by coma and inhibition of R.C.	Organophosphorus compund poisoning.
Mania – hallucinations – convulsions – hypotension – tachycardia – passive mydriasis – dry hot skin (fkush & fever) – constipation – urine retention – finally coma and inhibition of R.C.	Atropine
Apnea (due to paralysis of respiratory muscles) – hypotension – tachycardia – bronchospasm	Competitive neuro - muscular blockers as curare
Coma + inhibition of R.C. + pin point pupil	Morphine (see CNS)

- 1 The cause of death in acute toxicity is due to depression of R.C., i.e central respiratory failure.
- 2 Competitive neuro-muscular blockers cause peripheral respiratory failure but not central because they don't cross B.B.B
- 3 Organophosphorus compund poisoning cause both central and peripheral respiratory failure.
- 4 General rules for treatment of acute drug toxicity :

a.Stomach wash = gastirc lavage (if the drug is ingested**)

b.Care for respiration (endotracheal intubation – artificial respiration)

c.Antidote (if there is a specific antidote , e.g. atropine for organophosphorus poisoning , neostigmine for curare toxicity , physostigmine for atropine poisoning)

d.Symptomatic treatment (e.g. anticonvulsant as diazepam)

e.Increase (promote) renal excretion of the drug (by changing pH of urine : Acidification of urine in toxicity of basic drugs as amphetamine and ephedrine using ammonium chloride or ascorbic acid , Alkalinization of urine in toxicity of acidic drugs as salicylates (aspirin) using NaHCO_3 . The drug should be completely or partially excreted in urine unchanged)

**** In acute morphine toxicity stomach wash is performed although morphine is given by I.V. injection!! (see CNS)**

N.B : The size of the pupil is a useful diagnostic sign.

*** Therapeutic uses of choline esters**

Choline esters include:	Therapeutic uses:
1-Acetylcholine (natural)	None (must be given I.V. – very short duration – non-selective M-agonist)
2-Methacholine	1.Provocative test in diagnosis of bronchial asthma 2.P.V.D. 3.P.A.T 4.Provocative test in diagnosis of paroxysmal type of pheochromocytoma
3-Carbachol 4-Bethanechol	1.Glucoma (eye drops) 2.Non-obstructive post-operative paralytic ileus 3.Non-obstructive post-operative (or post-partum) urine retention
5-Succinylcholine (Depolarizing neuro – muscular blocker)	1.Adjuvant to general anaesthesia 2.Endotracheal intubation

N.B. : - All except Acetylcholine are synthetic.

- All are quaternary ammonium compounds.
- All except succinylcholine are parasympathomimetic.

Causes & Examples of Cross allergy

1-Similarity in the chemical structure of different drugs e.g.

- _ Penicillins & Cephalosporins
- _ Sulphonamides & thiazide diuretics, loop diuretics, Carbonic anhydrase inhibitors, & Sulphonylureas.

2- Similarity in the mechanism of action e.g.

- _ Aspirin & other NSAIDs (except paracetamol):Bronchial asthma

Drugs that should never be stopped SUDDENLY (abruptly)

1. **β -blockers** : sudden withdrawal causes rebound tachycardia , arrhythmia , angina & even acute myocardial infarction
2. **Clonidine** (and other selective α_2 -agonists) : sudden withdrawal causes “rebound hypertension” which is treated by giving clonidine again or by α_1 - blocker $\pm$ β -blocker or labetalol but never use non-selective β -blocker alone
3. **Noradrenaline IV infusion** : sudden withdrawal cause “rebound hypotension”
4. **Corticosteroids** : sudden withdrawal after chronic use causes “Acute Addisonian crisis”

Drugs and pheochromocytoma

Drugs used in treatment of pheochromocytoma (If inoperable)

- 1 **α_1 -Blockers** , especially phenoxybenzamine because it is a non-competitive irreversible blocker and is the most potent α -Blocker.

2 **Labetalol** ($\beta_1 + \alpha_1$ Blocker).

3 **β -Blockers** may be added to α -Blocker but never use non-selective β -Blockers (as propranolol) Alone as they cause more hypertension due to unopposed α -effect.

N.B. α -blockers may be also used pre-operative and intra-operative to avoid elevation of B.P during excision of pheochromocytoma.

Drugs used in diagnosis of pheochromocytoma

1. **α -Blockers** as phentolamine (Regitine test) Marked in B.P in sustained pheochromocytoma.
2. **Clonidine** (Clonidine suppression test) can't release of catecholamines in sustained pheochromocytoma.
3. **Methacholine and Histamine** release of catecholamines of B.P (instead of hypertension in other patients).
This is a "Provocative test" which is obsolete.

Drugs contraindicated in pheochromocytoma

1. **Guanethidine** (inhibit uptake 1 of noradrenaline sustained action of noradrenaline on post-synaptic α_1 -receptors on B.Vs more in B.P)
2. **Non-selective β -Blockers** if used alone (see before)

3. α_1 -Agonists

Drugs and body characters

A- Drugs causing alopecia

1- Anticancer drugs.

2- Heparin (anticoagulant).

3- Colchicine (treatment and prophylaxis of acute gouty arthritis).

4- Sodium Valproate (broad spectrum antiepileptic).

5- Oxazolidinediones (antiepileptics in petit-mal epilepsy).

6- Interferons (in treatment of Hepatitis C virus "HCV").

B- Drugs used in treatment of alopecia

1 . Minoxidil sulphate

2. Pilocarpine

C- Drugs causing hirsutism

1- Androgens.

2- Progesterone (in contraceptive pills).

3- Phenytoin (antiepileptic).

N.B: Minoxidil causes "Hypertrichosis".

D- Drugs causing Gynecomastia

- 1 **Digitalis** (due to steroid structure)
- 2 **Spironolactone** (due to steroid structure)
- 3 **Reserpine**
Due to decrease dopamine in CNS increase prolactin
- 4 **α -methyl dopa**
- 4 **Ketoconazole** (antifungal , decrease synthesis of androgens)
- 5 **Cimetidine** (H_2 -blocker , used in treatment of peptic ulcer , causes anti-androgenic action)
- 6 **Estrogen** (given to males for treatment of cancer prostate)

Drug groups

-zoline group

- 1 **Naphazoline**
- 2 **Tetrahydrozoline** α_1 -Agonists , used locally as nasal decongestants
- 3 **Xylometazoline**
- 4 **Tolazoline** α -blocker , causes nasal congestion

-lol group:

- 1- **β -Blockers** (Propranolol-Nadolol-Atenolol-Esmolol-.....)(Butoxamine is selective β_2 -Blocker)

-zosin group = selective α_1 -blockers

1-Prazosin

2-Terazosin

3-Doxazosin (*Tamsulosin = selective α_{1A} -blocker used in prostatic hyperplasia*)

-nidine group = α 2-Agonists

1 Clonidine (*anti hypertensive*)

2 Apraclonidine (*Used in glaucoma*)

3 Brimonidine

4-Tizanidine (*central skeletal muscle relaxant*)

-zepine group = selective M1-blocker

(useful in treatment of peptic ulcer)

1-Pirezepine

2-Telenzepine

-stigmine= carbamates , reversible anticholine-esterases

:

1-Physostigmine

2-Rivastigmine (*in Alzheimer*)

3-Neostigmine (*In myasthenia gravis*)

4-Pyridostigmine

-triptan group

used in acute migraine headache , agonists on 5HT1D

1-Sumatriptan

2-Rizotriptan

3-Zolmitriptan

4-Ranitriptan

-tropium group

= Atropine substitutes in bronchia asthma

1-Ipratropium

2-Oxytropium

3-Tiotropium

-tropine group = Atropine substitutes

1 Benzotropine *(in Parkinsonism)*

2 Homatropine *Mydriatics*

3 Eucatropine

-curium and curonium group=Competitive neuro-muscular blockers

1-Atracurium

2-Cis-atracurium

3-Mivacurium

4-Pancuronium

5-Vecuronium

6-Alcuronium

-tidine group = H2-Blockers used in peptic ulcer

1-Cimetidine (+ HME inhibitor + Gynecomastia and infertility)

2-Famotidine

3-Ranitidine

4-Nizatidine

-setron group = 5HT3-Antagonists

used as anti-emetics in cancer chemotherapy and radiotherapy

1-Ordansetron

2-Granisetron

3-Tropisetron

-lukast group = Leukotriene receptor antagonist

used in prophylaxis of bronchial asthma

1=Montelukast

2-Zafirlukast

-zolamide group = Carbonic Anhydrase Inhibitors

1-Acetazolamide

2-Methazolamide *See diuretics*

3-Ethoxzolamide

4-Dorzolamide *(eye drops in glaucoma)*

-dipine group = Dihydropyridine calcium channel blockers

(cause arteriodilatation more than cardiac dep.)

1-Nifedipine

2-Amlodipine

3-Nimodipine

4-Felodipine

5-Nicardipine

6-Isradipine

-pril group = ACE Inhibitors

1-Captopril

2-Lisinopril

3-Enalapril

-sartan group = ARBs (Angiotensin-Receptor Blockers)

1 Losartan

2 Valsartan

3 Candesartan

4 Telmesartan

-caine group = Na⁺ channel blockers acting as local anaesthetics

1-Procaïne

2-Tetracaine

3-Lidocaine (which is also antiarrhythmic)

Take care :

?? Butyryl choline esterase = Pseudocholine esterase

?? Scopolamine = Hyoscine

? Suxamethonium = Succinyl choline

?? Isoproterenol = Isoprenaline

?? Epinephrine = Adrenaline

?? Norepinephrine = Noradrenaline

G-protein coupled receptors

G_s ???? Stimulation of adenyl cyclase (A.C.) enzyme increase cAMP

1-All β -receptors (β_1 , β_2 , β_3)

2- H₂-receptors (in heart, parietal cells of stomach, B.Vs)

G_q Stimulation of phospholipase C (PLC)

increase Diacyl glycerol (DAG) and inositol triphosphate (IP₃) increase Ca²⁺ spasmogenic
Except in endothelium of B.Vs release of nitric oxide increase cGMP V.D.

1 α_1 -receptors

2 M₁-receptors

3 M₃-receptors

4 H₁-receptors (in smooth muscle fibres as bronchi-B.Vs-skin)

- 5 *5HT₂-receptors (in CNS-smooth muscle fibres as bronchi-platelets)*
- 6 *AT₁-receptors (AT II acts on AT₁-receptors V.C , increase aldosterone , increase sympathetic activity and trophic changes in heart and B.Vs)*

Gi Inhibit adenyl cyclase decrease cAMP

- 1 *α₂receptors (presynaptic-CNS-inhibit renin secretion)*
- 2 *M₂-receptors (Heart-presynaptic)*
- 3 *5HT₁-receptors (in CNS)*
- 4 *H₃-receptors (presynaptic-CNS)*

Therapeutic uses of Ergot Alkaloids

1. *Acute attack of Migraine headache :
Ergotamine , Dihydroergotamine , cafergot*
2. *Prophylaxis of migraine headache : Methysergide (anti-serotonin)*
3. *Prevention & treatment of post-partum haemorrhage*
4. *Involution of the uterus after delivery Ergomrine &*
5. *Diagnosis of Prinzmetal angina Methylergometrine*
6. *Senile cerebrovascular insufficiency: Dihydroergotoxine*
7. *PVD : Dihydroergotoxine*
8. *Parkinsonism Bromocriptine*
9. *Hyperprolactinemia in males and females (D₂-agonist that crosses BBB)*

